

Lee, Jong Y.

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Amendments to the Specification

Please replace the paragraph beginning at page 2, line 6 with the following paragraph. The underlined text shows the amendment to the paragraph.

EpoR cDNA has been isolated recently from mouse liver, Tojo et al., *Biochem. Biophys. Res. Comm.* 148: 443-48 (1987) and from human fetal liver. Jones et al., *Blood* 76:31-35 (1990); Winkelmann et al., *Blood* 76:24-30 (1990). The full length EpoR cDNA sequence is shown in the Sequence Listing as SEQ ID NO: 4. The human cDNA encodes a polypeptide chain of MW .about.55 kDa and having about 508 amino acids. Genomic clones of human EpoR have been isolated and sequenced. Penny and Forget, *Genomics* 11:974-80 (1991); Noguchi et al., *Blood* 78:2548-2556 (1991). Analysis of the coding sequence predicts about 24 amino acid residues in a signal peptide, about 226 amino acids in an extracellular domain, about 23 amino acids in a membrane-spanning domain, and about 235 amino acids in a cytoplasmic domain. D'Andrea and Zon, *J. Clin. Invest.* 86:681-687 (1990); Jones et al., *Blood* 76:31-35, (1990); Penny and Forget, *Genomics* 11: 974-80 (1991). The mature human EpoR protein has about 484 amino acids. All human erythroid progenitor cells have been shown to contain Epo receptors. Binding of Epo appears to decline as erythroid progenitor cells mature, until Epo receptors are not detectable on reticulocytes. Sawada et al., *J. Clin. Invest.* 80:357-366 (1987). Sawada et al., *J. Cell. Physiol.* 137:337 (1988). Epo maintains the cellular viability of the erythroid progenitor cells and allows them to proceed with mitosis and differentiation. Two major erythroid progenitors responsive to Epo are the Burst-forming units-erythroid (BFU-E) and the Colony-forming units-erythroid (CFU-E). The Epo receptor number correlates very well with the response to Epo in normal BFU-E and CFU-E. Epo receptor numbers appear to decline after reaching the peak receptor number at the CFU-E stage in human and murine cells. Sawada et al., *J. Clin. Invest.* 80:357-366 (1987); Landschulz et al., *Blood* 73:1476-1486 (1989). The recovery of Epo receptors after removal of Epo appears to be dependent on protein synthesis, which suggests downregulation of Epo receptor by degradation, and the subsequent upregulation of receptors by the new synthesis of receptors when Epo is removed. Sawyer and Hankins, *Blood* 72:132 (1988). Studies of Epo receptors on megakaryocytes and erythroid progenitors suggest that there is a link between the regulation of erythropoiesis and thrombopoiesis, in that stimulation of cell

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division by both cell types is controlled by Epo receptor numbers. Berridge et al., *Blood* 72:970-977 (1988). Although the Epo receptor has been cloned, the precise mechanisms involved in binding of Epo to Epo receptors and the relationship to subsequent erythropoietic processes are not known.